Photocatalysis

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Photoredox Catalytic α-Alkoxypentafluorosulfanylation of α-Methyl- and α-Phenylstyrene Using SF_6

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Abstract: *SF_6 was applied as pentafluorosulfanylation reagent to prepare ethers with a vicinal SF_5 substituent through a one-step method involving photoredox catalysis. This method shows a broad substrate scope with respect to applicable alcohols for the conversion of α-methyl and α-phenyl styrenes. The products bear a new structural motif with two functional groups installed in one step. The alkoxy group allows elimination and azidation as further transformations into valuable pentafluorosulfanylated compounds. These results confirm that non-toxic SF_6 is a useful SF_5 transfer reagent if properly activated by photoredox catalysis, and toxic reagents are completely avoided. In combination with light as an energy source, a high level of sustainability is achieved. Through this method, the proposed potential of the SF_5 substituent in medicinal chemistry, agrochemistry, and materials chemistry may be exploited in the future.*

Pentafluorosulfanylation (SF_5) chemistry has remained a challenging and difficult task since the initial report on CF_3SF_5 by Cady in 1950.[1] This lack of modern methods is astonishing considering the proposed physicochemical profile of the SF_5 substituent when added to small organic molecules.[2,3] For example, exchange of the widely used CF_3 substituent that is bioisosteric to CH_3 with a SF_5 substituent in the anoretic norfenfluramine induces a dramatic change in the pharmacological profile.[4] Further evidence for a benign profile of organic SF_5 compounds has been reported.[5] These features predict great potential for this functional group in chemistry.[6] However, the accessibility of SF_5 compounds is still rather difficult even though a mild synthesis starting from disulfides has been established by Umemoto and co-workers in 2012[7] and further facilitated by Pitts, Togni, and co-workers quite recently.[8] However, formation of the C–S bond still requires the use of extraordinarily toxic reagents, like S_2F_{10}, and the mixed-sulfur halogenides SF_5Cl and SF_5Br.

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In contrast, reports on non-toxic SF_6 in synthesis are rare although this would have strong environmental advantages.[9–15] SF_6 is still indispensable as an insulating gas in technical applications, like high-voltage gears, and as a protecting gas in the production of metals. SF_6 acts as an extremely potent greenhouse gas,[16] so the use of SF_6 as chemical reagent would be sustainable because the gas would be trapped and converted into potentially valuable chemical building blocks.

In general, the use of SF_6 as an SF_5 transfer reagent is difficult due to its alternating bond-dissociation enthalpies.[17] In particular the electron-excess-dependent fragmentation channels of the SF_6 radical anion have hampered proper activation by photoinduced single-electron transfer.[18–23] The dominant channel of activation at low electron excess energies is fragmentation into SF_4 and a fluoride anion.[18,22,23] This mode of reactivity was explored recently by Jamison and McTeague, as well as by Rueping and co-workers, who reported deoxyfluorination-type chemistry under photoredox conditions (Figure 1).[12,13] We unlocked the complementary mode of activation of SF_6 for pentafluorosulfanylation of α-substituted styrenes.[11]

Photoredox catalysis applies light as an energy source for organic reactions.[24–35] Herein, we report an advanced photoredox catalytic method for the activation of SF_6, which not only pentafluorosulfanylates α-methyl- (**1**) and α-phenyl- (**2**) styrenes but additionally forms a C–O bond, which significantly broadens the synthetic scope and opens the way for the functionalization of SF_5 building blocks. In contrast to fluorination,[12,13] our approach precisely controls the local reductivity by N-phenylphenothiazine (**3**) as a strong photo-

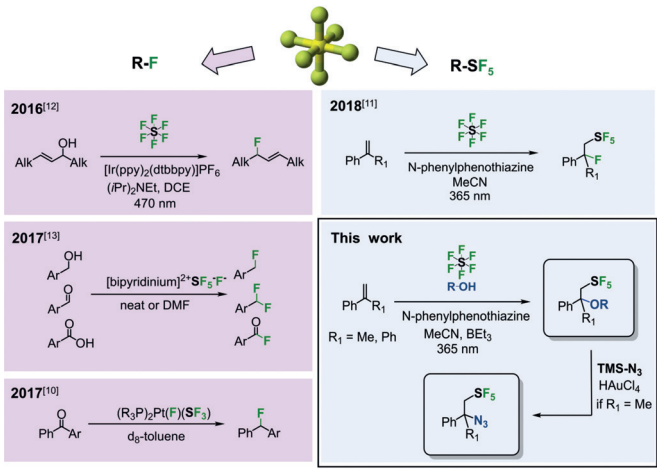

Figure 1. Overview of recent photochemical and chemical activation of SF_6 for deoxyfluorinations (left) and pentafluorosulfanylations (right).

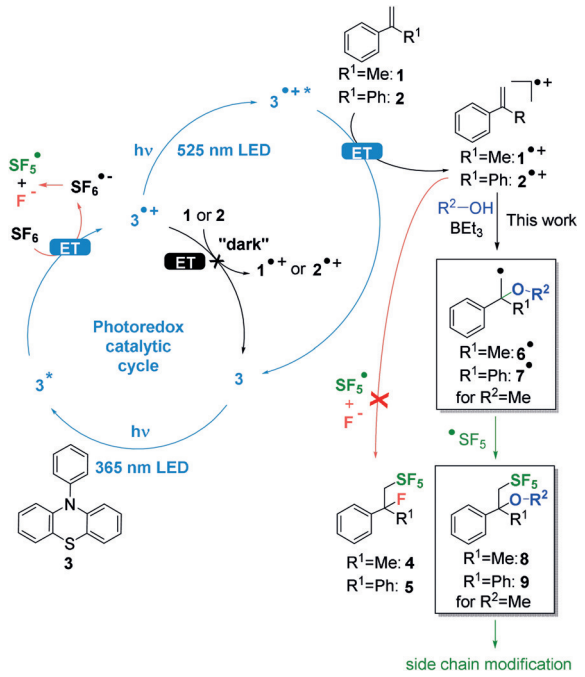

Figure 2. Proposed mechanism of photoredox catalytic activation of SF_6 by N-phenylphenothiazine (**3**) for pentafluorosulfanylation of α-methyl (**1**) and α-phenyl (**2**) styrene, and addition by fluoride as an internal nucleophile to give **4** and **5** or alcohols (R^2-OH) as external nucleophiles to give products **8** and **9** (shown for R^2 = Me).

redox catalyst[36] in order to transfer the SF_5 group to α-methyl- (**1**) and α-phenyl- (**2**) styrenes to yield products **4** and **5**.[11] Mechanistic investigations revealed a two-fold excitation process (Figure 2), similar to the conPET process reported by the König group.[37] Quenching of the excited state of **3** by SF_6 generates $SF_6^{\bullet-}$, which is fragmented by the electron excess energy into the SF_5 radical. The second electron transfer activates the substrates through formation of the radical cations $\mathbf{1}^{\bullet+}$ and $\mathbf{2}^{\bullet+}$. This process seems to be critical for successful pentafluorosulfanylation due to the high oxidation power of the SF_5 radical. The simple addition of MeOH to the reaction mixture consisting of **1** or **2**, catalyst **3**, and SF_6 in MeCN yielded the SF_5 methyl ethers **8** or **9**. The previously observed dimerization of **2**[11] was almost completely suppressed, which makes the fast trapping of $\mathbf{2}^{\bullet+}$ by MeOH very likely. The final step for pentafluorosulfanylation is the simple trapping of the resulting radicals $\mathbf{6}^{\bullet}$ or $\mathbf{7}^{\bullet}$, respectively, by the remaining SF_5 radical. The competing nucleophilic attack by in situ generated fluoride anions could be reduced by the addition of a Lewis acid. The addition of 10–20 mol% BEt_3 almost completely suppressed the formation of the vicinal fluoride **5** by trapping available fluoride anions in the solution. This is important for the preparation of a broader variety of SF_5 compounds with alcohols as external nucleophiles. Further functional groups in the side chains of these alcohols give access to versatile SF_5 building blocks.

We optimized the reaction conditions for **2** (Table 1). The initial yield of 29% of **9** (determined by GC-FID) was achieved with 10 mol% photocatalyst **3** and 5 equiv of MeOH in a 0.1M solution of **2**. The pressure of SF_6 was adjusted to

Table 1: Photoredox catalytic pentafluorosulfanylations of **2** to the methoxylated **9**.

Entry	Conditions[a]	[**2**] [M]	MeOH [equiv]	Yield [%]
1	365 nm	0.10	5	29
2	365 nm	0.10	10	44
3	365 nm	0.20	10	53
4	no light	0.10	10	no reaction
5	no catalyst	0.10	10	no reaction

[a] General reaction conditions: 20 mol% BEt_3, 20°C, 2.8 bar SF_6, 368 nm, 22 h in MeCN. Yields determined by GC-FID.

2.8 bar (3.1 mmol) by a gas measure apparatus. A higher amount of MeOH (10 equiv) increased the yield to 44%. Reducing the catalyst loading to 5 mol% **3** decreased the yield to 35%. While dilution of the reaction mixture to 0.05M also decreased the yield, an optimized yield of 53% was observed using 0.2M solution of **2**. Higher concentrations did not further increase the yield. Additional control experiments were carried out before a broader substrate scope was investigated. The use of methoxide as a strongly basic nucleophile caused a collapse in reactivity and **9** was not observed. As expected, no product was observed during control reactions in the absence of light or catalyst **3**, nor in the absence of MeOH. Finally, we explored the effect of BEt_3. While the selectivity was dramatically increased by BEt_3 (see above), the yield of **9** could not further be increased by the investigated range of 0–40 mol% BEt_3. This indicated a passive interaction in the mechanism and deactivation of the generated fluoride anion by the Lewis acidic boron. The precise active species could not be identified although the formation of an intermediate alcohol coordination complex is likely based on previous observations by Renaud and coworkers.[38] The model reaction was also performed on a scale of 1.00 mmol of **2**, which gave a yield of 45% for **9** with a higher pressure of SF_6 (5.5 bar), while the excess of SF_6 could be reduced to 6.1 equiv. The preparative isolation of **9** in 40% yield gave a pure product sample and allowed us to validate both the structure by NMR and XRD (Figure 3) and the applied ^{19}F-NMR quantification method. It is important to mention here that **8** or **9** are not produced by the reaction of the fluoride addition products **4** or **5** with methoxides, including $Ca(OMe)_2$, KOMe and LiOMe, and with BEt_3 (Figures S166–S173).

The substrate scope for the conversion of **1** and **2** is broad since a variety of functionalized alcohols, like branched alkohols, alkenols, internal and terminal alkynols, sterically demanding cyclopentanols, cyanoalcohols, and even allenes, were tolerated to give products **8**, **10**–**18** and **19**–**27** (Figure 3).

The photoredox catalytic method is limited, of course, to the use of non-oxidizable alcohols. Phenyl alcohols were not accepted, likely due to predominant oxidation by the catalyst **3**. Even more complex molecules like spiroethers were obtained through an intramolecular addition, yielding **29** in 26% yield. Full conversion of the starting materials, however, is problematic due to the aggressive reaction conditions and photocatalyst decomposition. Increased photocatalyst concentrations cause overreduction of the transients. Another competing reaction is the direct addition of alcohols to the

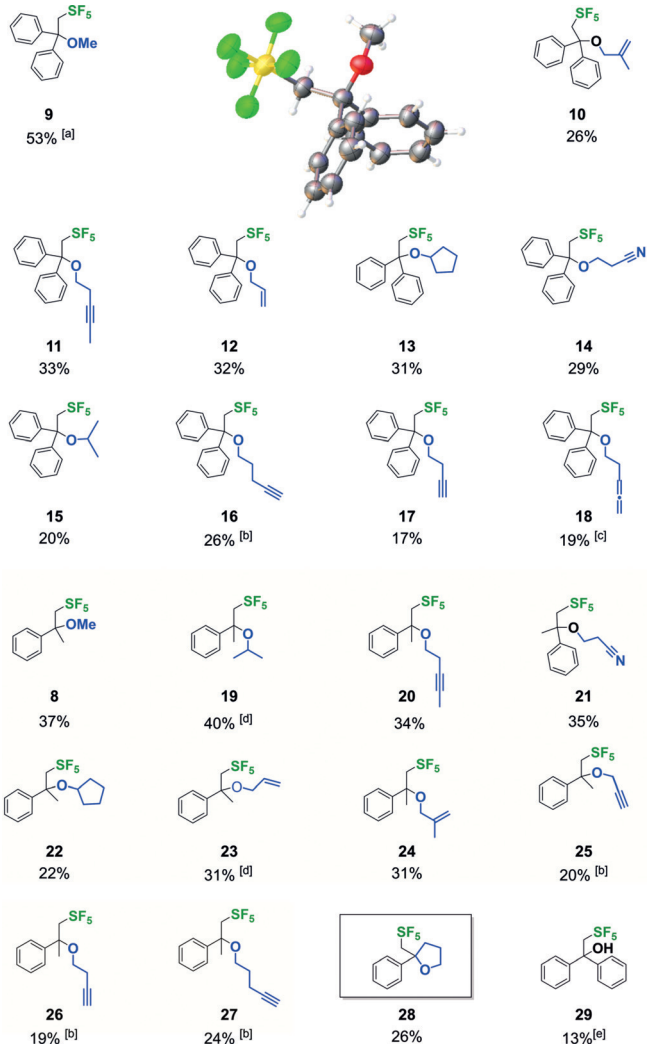

Figure 3. Substrate scope for the for the pentafluorosulfanylation of **1** and **2** and XRD structure of product **9**. Yields were determined by ^{19}F-NMR spectroscopy in the crude reaction mixture. General reaction conditions: 0.20 mmol, 0.20 M in MeCN, 10 mol% **3**, 10 mol% BEt_3, 22 h, 20 °C, 2.8 bar (15 equiv) SF_6, 368 nm. [a] Yield determined by GC-FID, 20 mol% BEt_3 used. [b] 3.0 equiv alkynol. [c] 0.15 M, 14 equiv. allene. [d] 1.00 mmol scale. [e] Prepared with 1-ethinyl-1-cyclopentanol.

substrates as well as in situ hydrolysis of the products probably due to the formation of oxophilic sulfur species. Nevertheless, we found a remarkably broad acceptance of various alcohols for the alkoxylation of **1** and **2**, and the obtained yields between 13% and 53% should be viewed in the context of the fact that compounds **10**–**28** were not previously synthetically accessible and bear a new and doubly functionalized structural motif. Additionally, our results show an orthogonal reactivity by the SF_5-radical pathway, which allows the use a large excess (10.0 equiv) of alcohol without fully quenching of the reactive transient by deoxyfluorination.[12,13] While the use of water as a nucleophile shut down the reaction, the use of tertiary alcohols favored the formation of alcohol **29**.

DSC experiments revealed a boiling point for **8** of about 18 °C (Figure S158) and a melting point for **9** of 125 °C (Figures S159 and S160). Compounds **8** and **9** were photochemically stable during irradiation (365 nm, 24 mM in DMSO, Figures S162 to S165) for at least 62 h. Compounds **8** and **9** were stable at 75 °C in DMSO (24 mM); at 125 °C **8** showed a half-life of 68 min and **9** a half-life of 84 min under air (Figures S161). This demonstrates sufficient stability for further chemical transformations, which we investigated: 1) Methoxylated **8** and **9** were successfully converted into the vinylic and allylic SF_5 compounds **30** and **31** by the oxophilic Lewis acid $BF_3{\cdot}Et_2O$ (10 equiv) in $CDCl_3$. The ^{19}F-NMR kinetic measurements showed remarkably fast conversion in both cases into the elimination products **30** and **31** with yields of more than 98% in under 30 min (Figure 4, top). 2) Finally, we broadened the versatility of our method by conversion of the benzylic ether **8** into the corresponding azide **32**. This reaction required $HAuCl_4$ as the catalyst.[39] Instead of the favored elimination reaction (by considering acidity), the ^{19}F NMR spectra evidenced a clean an efficient conversion of 98% after 5 h (Figure 4, bottom). Compound **32** showed the characteristic IR signatures of both the azide stretch mode at 2109 cm^{-1} and the SF_5 signatures at around 813 cm^{-1} (Figure S156). It is important to mention here that such vicinal SF_5 azides could potentially be used for click-type cycloadditions or could serve as precursors for the corresponding amino acids.

In conclusion, we report herein a novel method to synthesize ethers with vicinal SF_5 substituent through a one-step method including photoredox catalysis. The products described herein bear a new structural motif with two functional groups, the SF_5 and the alkoxy substituents, and thereby represent important new SF_5 building blocks. Moreover, the alkoxy substituents allow further transformation by elimination and azidation. Our results complement the closed-shell deoxyfluorination-type photoredox chemistry of SF_6 and pave the way to use SF_6 as a highly valuable SF_5-transfer reagent if properly activated by highly reducing

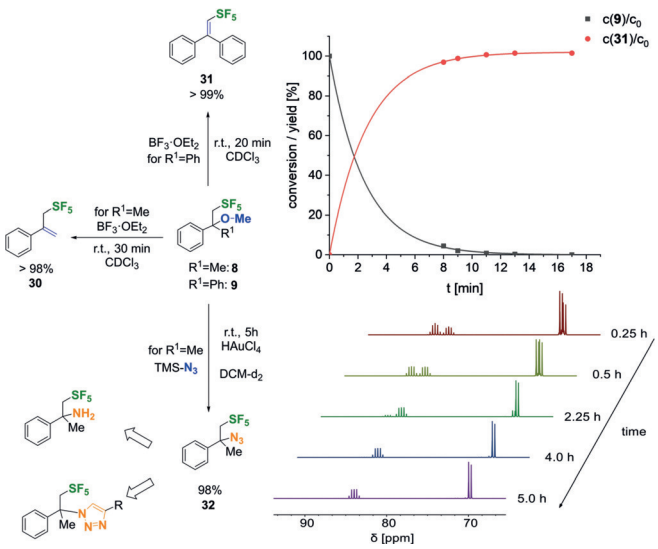

Figure 4. Top: Elimination of the methoxy substituent of **8** and **9** by 10.0 equiv $BF_3{\cdot}Et_2O$, and representative ^{19}F-NMR kinetics for the conversion of **9** to **31**. Bottom: Azidation of **8** to **32** (with potential following chemistry) and time-resolved ^{19}F-NMR spectroscopy analysis for the conversion of **8** into **32**.

photoredox catalysts. Our method not only tolerates protic groups and high concentrations of alcohols, but uses them as nucleophiles. Unfortunately, the presence of water as a nucleophile is strictly prohibited by irreversible sulfoxidation of the photoredox catalyst. Despite this restriction, the corresponding SF_5 alcohol can be prepared by the use of tertiary alcohols. Toxic reagents are completely avoided, and instead, non-toxic SF_6 is applied as a chemical reagent. Our vision is to reuse SF_6 after technical applications for chemical synthesis of valuable SF_5 molecules instead of simply destroying it, thereby enabling the proposed benign potential of the SF_5 substituent in medicinal, agricultural, and materials chemistry to be exploited in the future. In combination with light as an energy source, the basis for a high level of sustainability is set.

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Conflict of interest

D.R. and H.A.W. filed a patent application of the reported method.

Keywords: addition reactions · electron transfer · phenothiazine · photocatalysis · photochemistry

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